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Chemoprophylaxis of bacterial meningitis

Bacterial meningitis remains a life-threatening infection at any age. Approximately 80% of the patients belong to the paediatric age group and more than half of these children are less than two years old. Vaccines effective against all types of the three principal pathogens—*Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*—and immunogenic at any age including young infants, are the ultimate goal in order to reduce or even eliminate morbidity and mortality of this infection (Schaad, 1982, 1984). However, the currently available capsular polysaccharide preparations are far from such ideal vaccines (Mäkelä, 1982; Douglas *et al.*, 1983; Lepow & Gold, 1983; Hill, 1983; Peltola *et al.*, 1984). Close contacts of patients with invasive *H. influenzae* type b or meningococcal disease show a higher prevalence of nasopharyngeal carriage and are at considerably increased risk of contracting the disease (The Meningococcal Disease Surveillance Group, 1976; Ward *et al.*, 1979; Shapiro, 1982). Effective eradication of the nasopharyngeal bacteria by antimicrobial agents is possible. These facts explain the interest in chemoprophylaxis for the prevention of secondary cases in close contacts of patients with bacterial meningitis.

The key issue in the management of contacts remains clear education as to the need for close and careful surveillance because chemoprophylaxis will never result in absolute prevention of secondary cases. Throat or nasopharyngeal cultures do not contribute to the identification or management of contacts (Schaad, 1982, 1984).

The attack rate in close contacts of patients with meningococcal disease (meningitis or meningococcaemia) is 400 to 1200 times that of the general population (The Meningococcal Disease Surveillance Group, 1976; Shapiro, 1982; Peltola, 1983). Young children are at greatest risk, but secondary meningococcal disease occurs in all age groups. The candidates for prophylaxis are persons of all ages after contact with a case of invasive meningococcal infection within the week prior to the onset of disease in the household, day-care centre, military barracks or chronic care institution, and after intimate contact such as mouth-to-mouth resuscitation or kissing. Normal contact at work, at school, and by medical personnel does not represent a significant risk and does not require prophylaxis. Since the index patient often continues to be colonized with meningococci despite clinical cure and may therefore reintroduce the organism to his close contacts, the patient should probably also receive adequate chemoprophylaxis before discharged from the hospital. Before the emergence of sulphonamide-resistant meningococci, prophylaxis with sulphonamides was clearly effective both in preventing disease and eradicating the carrier state (Glasgow, 1980). Today, in non-endemic areas, approximately 25% of meningococci causing meningitis are resistant to sulphonamides. Penicillin, ampicillin, eryth-

romycin, tetracycline, chloramphenicol and cephalexin do not reliably eliminate nasopharyngeal colonization of meningococci, but minocycline and rifampicin are 80 to 90% effective. The high incidence of vestibular reactions associated with minocycline makes its use as prophylactic agent problematic. Thus despite potential emergence of resistance, possible side effects and drug costs, rifampicin represents the best choice for prophylaxis of meningococcal disease at present unless the strain in the index patient is known to be sensitive to sulphonamide. Both in Europe and North America, rifampicin doses of 10 mg/kg (maximum, 600 mg) given every 12 h are recommended for two to three days, the first dose given as soon as possible after diagnosis of the index case (Glasgow, 1980; Lambert, 1984; Schaad, 1982, 1984).

The rate of disease in previously healthy, close contacts of a patient with pneumococcal meningitis is not reported to be increased, and chemoprophylaxis is not necessary. However, predisposing factors for invasive pneumococcal diseases such as anatomical or immunological defects are well known and appropriate prophylaxis with vaccination and/or penicillin is indicated (Klein, 1981).

At present chemoprophylaxis of *H. influenzae* type b meningitis is a hotly debated issue. Recent reports from the United States demonstrated that household and day-care centre contacts of *H. influenzae* type b meningitis are at increased risk of developing the infection (Ward *et al.*, 1979; Granoff & Daum, 1980; Band, 1981; Shapiro, 1982). Over 50% of secondary cases occur in the first week after hospitalization of the index patient. In the age groups of less than two years and of two to four years, the attack rates were 200- to 400-fold higher than endemic rates in open populations. In contrast, secondary *H. influenzae* type b disease was rare in close contacts older than four years of age. Therefore, the candidates for prophylaxis are children less than four years of age after contact in the household, day-care centre or chronic care institution. Because asymptomatic carriers of any age may spread the bacteria to susceptible young children, eradication of nasopharyngeal colonization in all household members and day-care or institutional workers should theoretically be attempted. Chemoprophylaxis is also desirable for the index patients because they may remain colonized after adequate therapy for meningitis. Although several antimicrobial agents are effective against *H. influenzae in vitro*, many have been ineffective in eliminating nasopharyngeal carriage. These include ampicillin, cefaclor, erythromycin-sulfisoxazole, trimethoprim-sulphamethoxazole and trimethoprim-rifampicin. The majority of studies of rifampicin at 20 mg/kg orally in a single daily dose (maximum, 600 mg) for four days report a 90 to 95% efficacy in the eradication of nasopharyngeal *H. influenzae* type b colonization in household, day-care centre and institutional contacts (Shapiro & Wald, 1980; Murphy *et al.*, 1983). In a multicentre field trial coordinated by the US Centers for Disease Control, household and day-care centre contacts were randomized to receive rifampicin prophylaxis or placebo. There was a significant diminution in secondary cases among rifampicin recipients—no case among the 1112 rifampicin treated contacts versus four secondary cases among the 765 placebo-treated contacts (Band *et al.*, 1984). Based on this single preliminary experience the American Academy of Pediatrics (Committee on Infectious Diseases) formulated recommendations for the use of rifampicin prophylaxis of contacts of patients with *H. influenzae* infection (AAP, Red Book 1982) which recently were revised (AAP, 1984). This latest policy does not now include day-care centre and nursery school contacts ('individual' approach) and is concentrated on all contacts in households where there are children (other than the index case) less than four years old.

There are several factors inherent in rifampicin prophylaxis which in the opinion of many specialists in paediatric infectious diseases must exclude its routine recommendation at the present time (Shapiro, 1982; Daum & Halsey, 1982; Mann & Hull, 1983; Murphy *et al.*, 1983; Schaad, 1984): (1) Extended controlled experience on both epidemiology and rifampicin prophylaxis is needed from different countries including Western Europe, where day-care centres and nursery schools are less popular than in North America. (2) Failure of prophylaxis and recolonization at one to four weeks after rifampicin administration are most common in young children who are at greatest risk for disease. (3) Emergence of rifampicin-resistant *H. influenzae* type b strains after prophylaxis does occur. (4) Very large numbers of contacts should theoretically receive chemoprophylaxis in order to reduce secondary cases optimally. (5) Prevention and eradication of colonization may abort the physiological immunizing effect of inapparent infection. (6) Possible side effects and drug costs of rifampicin represent important logistic problems for widespread use of this agent.

Based on these six points it is concluded, that routine use of rifampicin for prevention of secondary *H. influenzae* type b disease in close contacts is not indicated. Close and careful surveillance of the exposed children is essential. Prophylactic rifampicin may be prescribed for all household contacts (as soon as possible) and the index patient (before hospital discharge) if there are household members of less than four years of age and if there are special circumstances such as an already damaged child, profound fear or extremely crowded conditions.

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Hypoprothrombinemia caused by cephalosporins

Cephalosporin-induced hypoprothrombinemia has been reviewed about two years ago in this Journal (Smith & Lipsky, 1983). New information has rapidly accumulated since then, and many problems which allowed only speculation one year ago, can now be discussed on the basis of firm evidence. This leading article addresses the problem of whether cephalosporins cause hypoprothrombinemia by interfering with colonic microflora or with hepatic metabolism of vitamin K.

Clinical observations (Holt, Gorrochategui & Perez, 1981; Pakter *et al.*, 1982; Schwigon &